HFV-335

Date of Approval: NOV 18 2005

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-334

EQUIZONE 100
(phenylbutazone)

Powder

Horses

For oral use in horses for the relief of inflammatory conditions associated with the musculoskeletal system

Sponsored by:

A & G Pharmaceuticals, Inc.

2006-200-334

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. *GENERAL INFORMATION:*

a. File Number:	ANADA 200-334
b. Sponsor:	A & G Pharmaceuticals, Inc. 1030 West Commodore Blvd. Jackson, NJ 08527 Drug Labeler Code: 057699
Agent:	James H. Schafer, D.V.M. Schafer Veterinary Consultants, LLC 800 Helena Ct. Ft. Collins, CO 80524
c. Established Names:	Phenylbutazone
d. Proprietary Name:	EQUIZONE 100
e. Dosage Form:	Powder
f. How Supplied:	2.2 lb (1 kg) jars
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	Each 10 grams of powder contains 1 gram of phenylbutazone
i. Route of Administration:	Oral
j. Species/Class:	Horses
k. Recommended Dosage:	Administer orally on a small amount of palatable feed 1 to 2 level scoops (using the scoop provided) per 500 pounds of body weight, but not to exceed 4 grams per animal daily. One level scoop contains 10 grams of powder equivalent to 1 gram of phenylbutazone. Use high dose for the first 48 hours, then gradually reduce to a maintenance dose.
l. Pharmacological Category:	Non-steroidal anti-inflammatory drug (NSAID)

m. Indications:	For the relief of inflammatory conditions associated with the musculoskeletal system in horses.
n. Pioneer Product:	Phenylbutazone Tablets, USP; phenylbutazone; NADA 091-818, Phoenix Scientific, Inc.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

On December 7, 1999, A & G Pharmaceuticals, Inc. was granted approval of a suitability petition (SP 99P-4167/CP 1) that requested a change in dosage form from that of the approved new animal drug. The pioneer product, NADA 091-818, is a tablet, whereas the generic product is a powder. To establish that the different oral dosage forms are bioequivalent and can be used interchangeably, the sponsor conducted an *in vivo* blood-level bioequivalence study comparing the generic product EQUIZONE 100 (phenylbutazone) powder to the reference product Phenylbutazone Tablets, USP. A separate palatability study was conducted to demonstrate that the generic phenylbutazone powder would be consumed when fed with a grain ration at the dose indicated on the product labeling. The studies are summarized below.

A. Blood-level Bioequivalence Study

Title of Study: "A Two-Way Single-Dose Bioequivalence Study with Oral Phenylbutazone in Healthy Horses." (Study No. C-0004)

Investigator(s): Colorado Animal Research Enterprises
Fort Collins, CO
(Animal phase)

PPD Development
Middleton, Wisconsin
(Analytical phase)

General Study Design:

1. Objective: Assessment of *in vivo* bioequivalence of A & G's formulation of Phenylbutazone Palatable Powder (test product) in horses compared to Phenylbutazone Tablets, USP, NADA 91-818, manufactured by Phoenix Scientific, Inc. of St. Joseph, MO (reference product). This study was conducted in accordance with Good Laboratory Practice Regulations (21 CFR Part 58).

2. Study Animals: Twenty-four domestic breed horses (12 non-pregnant females and 12 gelded males) were randomly assigned in equal numbers to either of two treatment sequences.

3. Treatment Groups: The study was of two-period crossover design. Group I received control product and Group II received test product in Period 1. Fourteen (14) days later, Group I received the test product and Group II received the control product as period 2.

No. of Horses	Treatment Design			
	Phenylbutazone Oral Dosage (mg/kg body wt.)	Period 1	Washout Interval Between Treatments	Period 2
6 male, 6 female	8.8 mg/kg	Product A	14 days	Product B
6 male, 6 female	8.8 mg/kg	Product B	14 days	Product A

Treatment codes A and B were randomly assigned to the drug products as follows:
A = Reference Article (Phenylbutazone Tablets, USP, 1 g/tablet)
B = Test Article (Phenylbutazone powder, 100 mg/g)

4. Dosage Form: A & G's generic Phenylbutazone Powder contains 1 grams of phenylbutazone per 10 grams powder (100 mg/g). The reference product Phenylbutazone Tablets, USP, NADA 91-818, manufactured by Phoenix Scientific, Inc. has a potency of 1 gram phenylbutazone per tablet.

5. Route of Administration: Test powder and control tablets were dispensed into gelatin capsules for oral administration. Horses were fasted for approximately 12 hours pre-dose to approximately 4 hours post-dose. Water was withheld for approximately 4 hours pre-dose and 4 hours post-dose.

6. Dosage(s): 8.8 mg per kg of body weight.

7. Pertinent Parameters Measured:
   a. Clinical Examinations and Observations – Prior to the onset of each period, each horse received a veterinarian-conducted physical examination in accordance with protocol specifications. General animal health status and conditions in the test facility were observed at least twice daily by animal technicians from the time of animal acquisition until the study concluded. Daily observations and body weight measurements did not result in reference or test article related findings.

   b. Analytical methods – Blood samples were collected at scheduled collection times. Plasma was harvested and assayed for phenylbutazone concentration. Individual plasma levels were tabulated and applicable pharmacokinetic parameters were calculated for horses receiving the test and control products.

c. Statistical analysis – Phenylbutazone concentrations in plasma extracted from blood samples were measured at appropriate intervals after treatment Maximum Concentration (C_{MAX}), Time to Maximum Concentration (T_{MAX}), Area Under the Curve (AUC).

Results: Differences in the pharmacokinetic parameters between Test and Reference products were statistically evaluated by means of 90% confidence intervals. Control and test product means for each parameter are provided below, along with the corresponding confidence intervals.

Variable	Test Mean	Control Mean	Lower CI	Upper CI
Log_e (Area Under Curve)	5.942	5.926	-7.11%	11.20%
Log_e (Maximum Concentration)	3.516	3.449	0.71%	15.09%
Time to Maximum Concentration (hours)	4.425 hrs	4.492 hrs	-19.96%	21.48%

Adverse Reactions: No adverse reactions to the test or reference product dosages were noted during this study.

Conclusions: Based on a criterion that the 90% confidence interval for the difference between product means be within ±80-125% of the reference product mean (for log transformed data), the test product was found to be bioequivalent to the reference product.

B. Palatability Study of Phenylbutazone Powder in Horses

Type of Study: Palatability Study

Investigator: J. Stanley Brown, D.V.M.
Columbus, NJ

General Design of the Investigation:

1. Objective: This clinical study was designed to determine the palatability of A&G Pharmaceutical, Inc.'s phenylbutazone oral powder when administered orally in a palatable grain rations to horses.

2. Study Animals: Fifty-eight (58) male and female Standardbred and Arabian horses approximately 2 to 15 years age at the time of treatment and weighing 750-1250 pounds were included in the study.

3. Dosage Form: A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder, an orally administered product which contains 10% phenylbutazone, was used as the test article for this study.

4. Route of Administration: Oral – The powder was administered in a palatable grain ration.

5. Dosage: A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder was administered at a rate of 2 grams of phenylbutazone per 500 pounds of body weight per day for two days. Half of the daily dose of powder was administered orally by mixing it in 2-3 pounds of their grain ration at each feeding.

6. Pertinent Parameters Measured:
   a) Health Examinations/observations – Prior to the onset of each period, each horse received a veterinarian-conducted physical examination in accordance with protocol specifications. Animals were monitored for about 45 minutes after each dosing for adverse reactions.

   b) Grain ration consumption – The amount of grain ration consumed within 30 minutes was recorded as 0%, 25%, 50%, 75% or 100% with "100%" indicating the entire grain ration was consumed. If animals did not consume 100% of the allotment of treated grain within the allowed time interval, the remainder was removed completely from the feed trough and measured in graduated measuring device.

   c) Data analysis – A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder was to be considered palatable when mixed in a grain ration if at least 75% of the treated feedings were consumed 100% by the participating animals in the 30-minute feeding period allowed.

Results: The horses completely consumed the medicated grain ration 80.4 percent of the times it was offered, fulfilling the criterion of the study that at least 75% of the treated feedings were consumed 100% by the participating animals in the 30-minute feeding period allowed.

Adverse Reactions: No adverse reactions to the test product were noted during this study.

Conclusions: Based on a criterion that the 90% confidence interval for the difference between product means be within ±80-125% of the reference product mean (for log transformed data), A & G Pharmaceuticals, Inc.'s phenylbutazone oral powder was found to be bioequivalent to the reference product.

The results from the palatability study indicate that A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder is palatable when fed with a grain ration at the 2 grams per 500 pounds of BW per day dosage.

3. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food producing animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human warnings are provided on the product label as follows: "Keep this and all medications out of the reach of children. Dispense in tight, child resistant containers."

4. AGENCY CONCLUSIONS:

This Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal, Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that EQUIZONE 100, when used under its proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic animal drug, EQUIZONE 100, were established by the demonstration of blood-level bioequivalence to the pioneer product, Phenylbutazone Tablets, USP, sponsored by Phoenix Scientific, Inc. under NADA 091-818. Palatability was also tested and found to be acceptable.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as follows:

Generic Labeling for ANADA 200-334:
EQUIZONE 100 (phenylbutazone)
Jar label – 2.2 lb (1 kg)
Outsert labeling

Pioneer Labeling for NADA 091-818:
Phenylbutazone Tablets, USP
Container label – 100 tablets
Package insert

lamination

INDICATIONS: Phenylbutazone is for the relief of inflammatory conditions associated with the musculoskeletal system in horses. In the treatment of inflammatory conditions associated with infections, specific anti-infective therapy should be used concurrently.

DOSAGE AND ADMINISTRATION: For Horses Only: Administer orally (using the 0.6 ounce (18 mL) scoop provided) on a small amount of palatable feed and mix well. Give 1 to 2 level scoops per 500 pounds of body weight, but do not exceed 4 scoops per animal daily. Use the high dose for the first 48 hours, then gradually reduce to a maintenance dose.

TAKE TIME OBSERVE LABEL DIRECTIONS

EQUIZONE 100™

(phen[redacted]one)

F[redacted]ly

NON-[redacted]SAID

CAUTION: [redacted] use by or on the [redacted]. Federal law prohibits the [redacted] product in female dairy [redacted]ge or older.

Net Cont[redacted]2 lb (1 kg)

ANADA 200-334, Approved by FDA

Each 10 grams of powder contains:
Phenylbutazone ..... 1 gram
One level scoop delivers 10 grams of powder.

RESIDUE WARNING: Do not use in horses intended for human consumption.
HUMAN WARNINGS: Keep this and all medications out of the reach of children. Dispense in tight, child resistant containers.

PRECAUTION: Concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored.

Store at room temperature, 15°-30°C (59°-86°F).

EQUIZONE 100™ is a trademark of A & G Pharmaceuticals, Inc.

Manufactured for
A & G Pharmaceuticals, Inc.
Jackson, NJ 08527

OPEN HERE

A&G Pharmaceuticals, Inc.

Lot No. Exp. Date

Iss. 7-05

varnish

chronic equine arthritis of long duration, fair results in severely bruised mare and poor results in two cases where the condition was limited to the third phalanx.

HOW SUPPLIED: EQUIZONE 100 Powder is supplied in 2.2 lb (1 kg) jars each containing a dispensing scoop. One level scoop delivers 10 grams of powder containing 1 gram of phenylbutazone.

Store at room temperature, 15°-30°C (59°-86°F).

References:

1. Kuzell, WC, Schaffarzick, RW, Naughler, WE, Gandia, C, and Mankle, EA: A.M.A. Arch. Inst. Med., 92:648 (1953).
2. Kuzell, WC, Schaffarzick, RW, Brown, B, and Mankle, EA: J.A.M.A., 149:729 (1952).
3. Kuzell, WC, and Schaffazick, RW: Calif. Med., 77:319 (1952).
4. Payne, RW, Shelter, MR, Farr, CH, Hellbaum, AA, and Ishmail, WK: J. Lab. Clin. Med., 45:331 (1955).
5. Fleming, J, and Will, G: Ann. Rheumat., Dis., 12:95 (1953).

4

6. Denko, CW, and Rumi, D: American Pract., 6:1865 (1956).
7. Fabre, J, et al: Semain. Hop. (Paris), 31:87 (1955).
8. Domenjoz, R, et al: Arzneimittel-Forsch. 5:488 (1955).
9. Wilhelmi, G, and Pulver, R: Arzneimittel-Forsch, 5:221 (1955).
10. Yourish, W, Paton, B, Brodie, B, and Burns, J: A.M.A. Arch. Ophth., 53:284 (1955).
11. Hazelton, LW, Tusing, TW, and Hollana, EG: J. Pharmacol. Exper. Ther., 109:387 (1953).
12. Ogilvie, FB, and Sutter, MD: Vet. Med. 62:492 (1967).
13. Camberos, HR: Rev. Med. Vet. (Buenos Aires), 38:9 (1956).
14. Sutter, MD: Vet. Med., 53:83 (1958).

Iss. 7-05

5

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Phenylbutazone ..... 1 gram
One level scoop delivers 10 grams of powder.

RESIDUE WARNING: Do not use in horses intended for human consumption.
HUMAN WARNINGS: Keep this and all medications out of the reach of children. Dispense in tight, child resistant containers.

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Store at room temperature, 15°-30°C (59°-86°F).

EQUIZONE 100™ is a trademark of A & G Pharmaceuticals, Inc.

Manufactured for
A & G Pharmaceuticals, Inc.
Jackson, NJ 08527

EQUIZONE 100™
(phenylbutazone)

Powder
For Oral Use In Horses Only

NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits the extralabel use of this product in female dairy cattle 20 months of age or older.

DESCRIPTION: Phenylbutazone chemically is 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione.

$C_{19}H_{20}N_2O_2$

Mol. Wt. 308.38

Each 10 grams of powder contains 1 gram phenylbutazone

1

INDICATIONS: Phenylbutazone is for the relief of inflammatory conditions associated with the musculoskeletal system in horses. In the treatment of inflammatory conditions associated with infections, specific anti-infective therapy should be used concurrently.

DOSAGE AND ADMINISTRATION: For Horses Only: Administer orally (using the 0.6 ounce (18 mL) scoop provided) on a small amount of palatable feed and mix well. Give 1 to 2 level scoops per 500 pounds of body weight, but do not exceed 4 scoops per animal daily. Use the high dose for the first 48 hours, then gradually reduce to a maintenance dose.

CONTRAINDICATIONS: Use with caution in patients who have history of drug allergy.

RESIDUE WARNING: Do not use in horses intended for human consumption.
HUMAN WARNINGS: Keep this and all medications out of the reach of children. Dispense in tight, child resistant containers.

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2

CLINICAL PHARMACOLOGY:
Phenylbutazone was first synthesized in 1949 and introduced into human medicine in 1949. Kuzell (1), (2), (3), Payne (4), Fleming (5) and Denko (6) demonstrated the clinical effectiveness of phenylbutazone in gout, gouty arthritis, acute arthritis, acute rheumatism and various other rheumatoid disorders in humans. Fabre (7), Domenjoz (8), Wilhelmi (9) and Yourish (10) have established the anti-rheumatic and anti-inflammatory activity of phenylbutazone. It is entirely unrelated to the steroid hormones.

Toxicity of phenylbutazone has been investigated in rats and mice (11) and dogs (12).

Phenylbutazone has been used by Camberos (13) in thoroughbred horses. Favorable results were reported in cases of traumatism, muscle rupture, strains and inflammations of the third phalanx. Results were not as favorable in the period treatment of osteoarthritis of the stifle and hip, arthrosis of the trapezious muscles and general arthritis. Sutter (14) reported a favorable response in

3

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Customer: A & G Pharmaceutical P.O. #: George CYREL #: 36399 (In)

Customer Service: Kathy Roper • kroper@tabcoinc.com

Date 07/05/05 07/12/05 08/03/05 08/23/05 09/20/05 09/21/05 09/28/05

Unwind #: 4

desc.: Equizone 100 size: 3.0 " x 7.75 "

varnish: [X] pattern [ ] flood

lamination: [X]

colors: black 283 blue pattern varnish lower section
lamination upper section

LABEL COPY

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AM/BT/AG/BUT/F/RX

PHENYLBUTAZONE TABLETS, USP 1 gram

NADA 91-818, Approved by FDA

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Phenylbutazone chemically is 4-butyl-1, 2 diphenyl-3, 5-pyrazolidinedione.

$C_{19}H_{20}N_2O_2$

Mol. Wt. 308.38

Each tablet contains 1 g of phenylbutazone

BACKGROUND PHARMACOLOGY: Phenylbutazone was first synthesized in 1948 and introduced into human medicine in 1949. Kuzell (1), (2), (3), Payne, (4), Fleming, (5) and Denko, (6) demonstrated the clinical effectiveness of phenylbutazone in gout, gouty arthritis, acute arthritis, acute rheumatism and various other rheumatoid disorders in humans. Fabre (7), Domenjoz, (8), Wilhelmi, (9) and Yourish, (10), have established the anti-rheumatic and anti-inflammatory activity of phenylbutazone. It is entirely unrelated to the steroid hormones.

Toxicity of phenylbutazone has been investigated in rats and mice (11), and dogs (12).

Phenylbutazone has been used by Camberos (13), in thoroughbred horses. Favorable results were reported in cases of traumatism, muscle rupture, strains and inflammations of the third phalanx. Results were not as favorable in the periodic treatment of osteo-arthritis of the stifle and hip, arthrosis of the trapezious muscles and general arthritis. Sutter, (14) reported a favorable response in chronic equine arthritis of long duration, fair results in severely bruised mare and poor results in two cases where the condition was limited to the third phalanx.

INDICATIONS: Phenylbutazone is for the relief of inflammatory conditions associated with the musculoskeletal system in horses.

DOSAGE AND ADMINISTRATION: For Horses Only: Orally 1 to 2 tablets per 500 pounds of body weight, but not to exceed 4 g per animal daily. Use high dose for the first 48 hours, then gradually reduce to a maintenance dose.

CONTRAINDICATIONS: Use with caution in patients who have history of drug allergy.

PRECAUTION: In the treatment of inflammatory conditions associated with infections, specific anti-infective therapy should be used concurrently.

WARNING: Not for horses intended for food.

HOW SUPPLIED: Tablets containing 1 gram of phenylbutazone are supplied in bottles of 100 tablets.

Store at controlled room temperature, 20° to 25°C (68° to 77°F)

References:

1. Kuzell, WC, Schaffarzick, RW, Naughler, WE, Gandia, C and Mankle, EA: A.M.A. Arch. Inst. Med., 92,646 (1953).
2. Kuzell, WC, Schaffarzick, RW, Brown, B and Mankle, EA: J.A.M.A. 149; 729 (1952).
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7. Fabre, J, et al: Semain. Hop. (Paris) 31; 87 (1955).
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10. Yourish, W, Paton, B, Brodie, B, Burns, J: A.M.A. Arch. Ophth., 53: 264 (1955).
11. Hazelton, LW, Tusing, TW and Hollana, EG: J. Pharmacol, Exper. Ther., 109; 387 (1953).
12. Ogilvie, FB and Sutter, MD: Vet. Med 52; 492-4 (1957).
13. Camberos, HR: Rev. Med. Vet. (Buenos Aries) 38: 9 (1956).
14. Sutter, MD: Vet. Med., 53; 83 (Feb. 1958).

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Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503